



السنة الثالثة

كيمياء العقاقير

د. عصام حسن آغا

ج 2

Digitalis lanata glycosides – Structure

بنية غليكوزيدات الديجيتال لاناتا

»» **Primary glycosides with acetylated sugar moieties.** غليكوزيدات اولية مع جزء مؤستل

»» **Major constituents:**

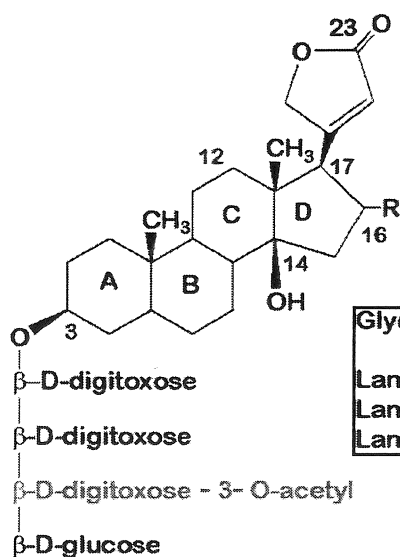
Primary glycosides	Secondary glycosides	Aglycones
Lanatoside A	Digitoxin	Digitoxigenin
Lanatoside B	Gitoxin	Gitoxigenin
Lanatoside E	Gitalexin	Gitalexigenin

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Digitalis lanata glycosides – Structure

بنية غليكوزيدات الديجيتال لاناتا



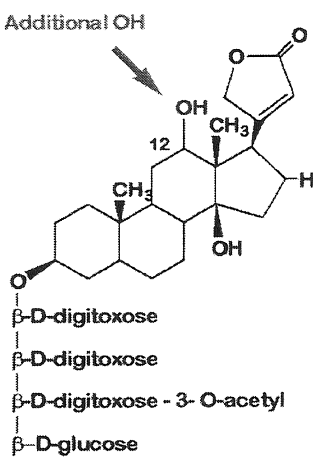
Glycoside	R	Aglycone
Lanatoside A	H	Digitoxigenin
Lanatoside B	OH	Gitoxigenin
Lanatoside E	CHO	Gitalexigenin

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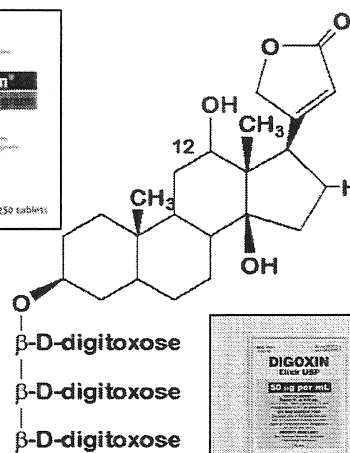
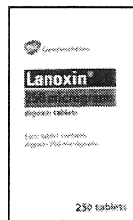
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Digoxin (Lanoxin®)

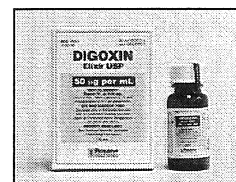
Additional OH



Lanatoside C



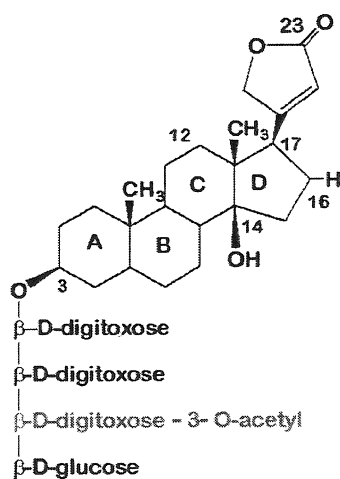
Digoxin



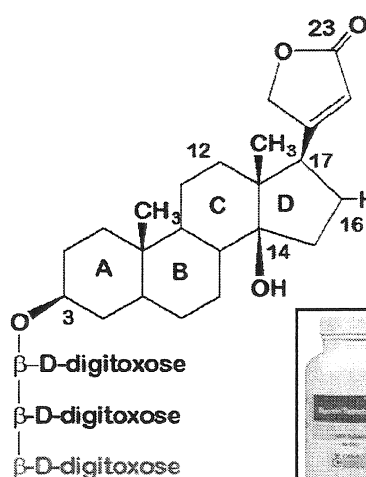
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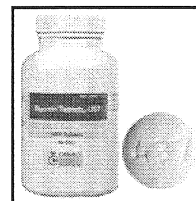
Digitoxin



Lanatoside A



Digitoxin



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Comparison between Digoxin & Digitoxin

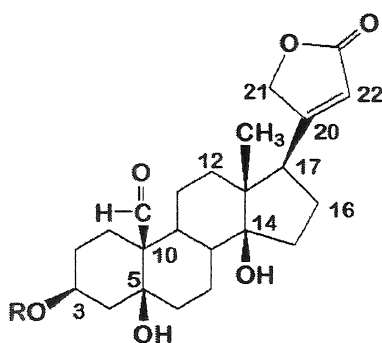
مقارنة بين الديجوكسين والديجيتوكسين

Name	Digoxin (Lanoxin®)	Digitoxin
Source	<i>D. lanata.</i>	<i>D. purpurea, & lanata</i>
Administration	Usually oral	Oral
Onset of action	After 30 min to 2 hours	After 1-4 hours
Peak	At 2 to 6 hours.	At 8 - 14 hours
Plasma half-life	30 to 40 hours	168 to 192 hours
Complete elimination after discontinuation of therapy	6 to 8 weeks	3 to 5 weeks
Full therapeutic effect	0.5-2ng / ml	14-26 ng / ml
Toxicity symptoms	2.5 ng / ml	35 ng / ml
Indication	When risk of intoxication is great, as it is relatively short-acting & more rapidly eliminated than digitoxin.	Recommended for patients with impaired renal function.

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Strophanthus kombe glycosides



Glycoside

R=sugar moiety

K-strophanthoside

Cymarose-β-glucose-α-glucose

K-strophanthin-B

Cymarose-β-glucose

Cymarol

Cymarose

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K-strophanthoside (Stroposide)

Source:

Principal primary glycoside in *S. kombe* & *S. hispidus*.

Hydrolysis:

Enzymatic (gradual)

- ❖ K-strophanthoside + α -Glucosidase \rightarrow terminal α -glucose + K-strophanthin-B
- ❖ K-strophanthin-B + strophanthobiase \rightarrow β -glucose + cymaridin

Uses:

K-strophanthin-B (like ouabain) is mainly used for intravenous therapy.

Chemical tests:

- + 66% $\text{H}_2\text{SO}_4 \rightarrow$ emerald green color.
- Solution in H_2O + FeCl_3 + $\text{H}_2\text{SO}_4 \rightarrow$ red color \rightarrow green color.

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Strophanthus gratus glycosides- Ouabain (G-strophanthin)

Source: Seeds of *S. gratus* (Apocynaceae).

Hydrolysis: \rightarrow ouabagenin + rhamnose.

Structure:

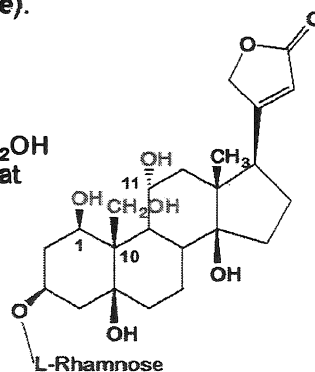
1. Most polar cardiac glycoside.
2. Characterized by the presence of $-\text{CH}_2\text{OH}$ group at C-10 & additional OH groups at C-1 & C-11.

Chemical test

1. + 66% $\text{H}_2\text{SO}_4 \rightarrow$ pink color \rightarrow green fluorescence.
2. + Froehde's reagent, evaporate + conc. $\text{H}_2\text{SO}_4 \rightarrow$ blue color.

Uses

Used as cardiotonic & antiarrhythmic agent.



Ouabain

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Squill glycosides- White squill

Chemical test

1. Squill glycosides give positive tests for the steroidal moiety only, as they neither contain a pentacyclic lactone ring with a $-\text{CH}_2$ group (c.f. cardenolides) nor a 2- deoxy sugar in their sugar moiety.
2. Squill glycoside or aglycone + acetic anhydride + $\text{H}_2\text{SO}_4 \rightarrow$ blood red \rightarrow blue \rightarrow bluish green color.

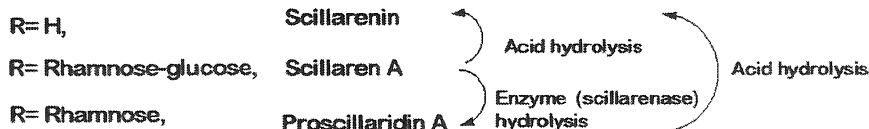
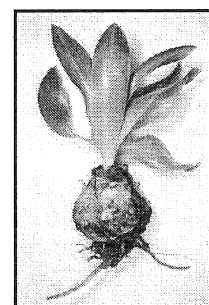
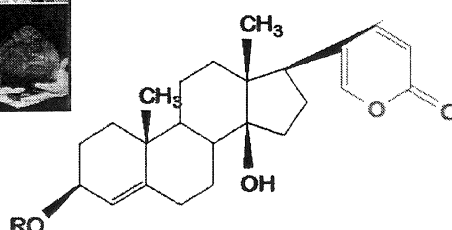
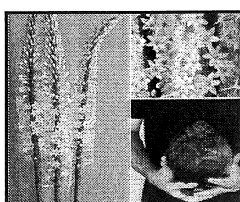
Uses

- » Expectorant & emetic (mainly due to saponin), cardiotonic & diuretic.
- » Cardiac glycosides of squill exert a rapid cardiotonic action & are rapidly eliminated & less potent than other cardiac glycosides.

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Squill glycosides- White squill



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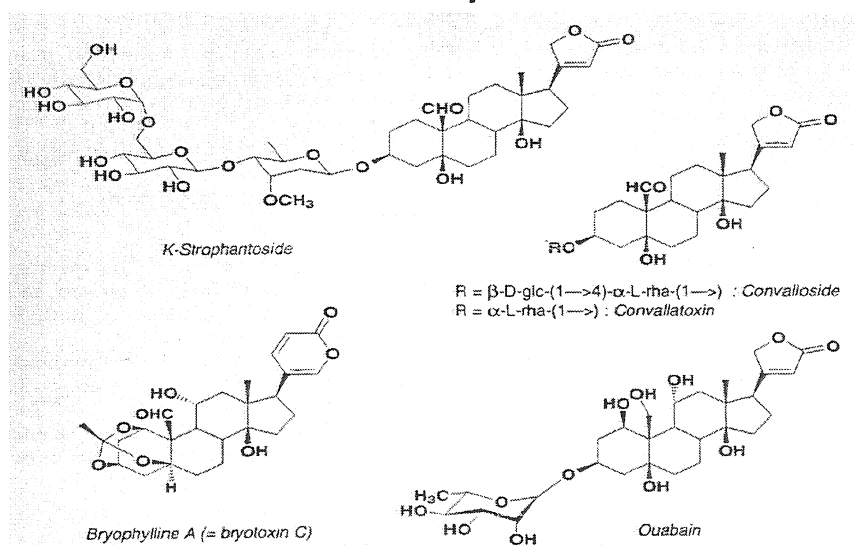
Red squill

- »» Bulb & bulb scales of red variety of *U. maritima*, used as rat poison (rodenticide)
- »» Should not be present in medicinal squill
- »» Detected by presence of red, pink, or purple epidermal or parenchymatous tissues.

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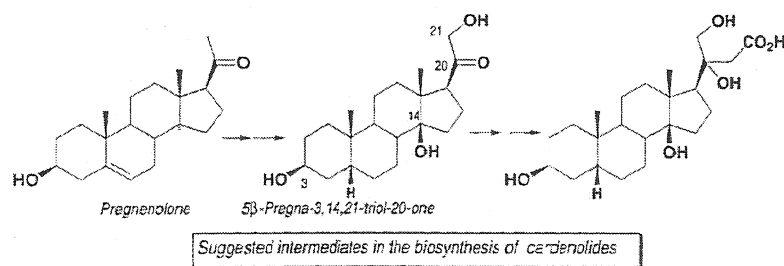
Cardiac Glycosides



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Biosyntheses of Cardinolides



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Characterization of cardiac glycosides

- Extraction
- Purification
- (pulverized drug + ethanol 50%, and lead acetate solution, boiling, cooling, elimination the residue by centrifugation. The supernatant layer extracted with CHCl₃, Chloroform solution used in the test.)

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Color Reactions

- **Color Reactions of the Sugers:**
 1. Xanthydrol or Pesez reaction (adding xanthydrol to the glycoside solution in concentrated acetic acid, heating, red color.
 2. Keller –Kiliani reaction: adding of concentrated sulfuric acid, traces of ferric salts to a glycoside solution in concentrated acetic acid, reddish-brown ring develops and the acetic acid solution turns slowly blue-green.

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Color Reactions

- **Color Reactions of the Aglycones:**
 1. Steroids Reactions
 2. Kedde reaction (Orange color with di-nitro Benzoic acid) and Baljet Reaction (orange color with picric acid): Aromatic nitro derivatives gives in an alkaline medium, deeply colored adduct in the presence of unsaturated lactones rings.

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Color Reactions

- **Fluorescence Reactions:** Cardiac glycosides form, under acidic conditions, fluorescent dehydrated derivatives: 14-dehydro derivatives, and in the case of Aglycones substituted at C-16, 14, 16-didehydro derivatives. (resulting trienone has three double bonds conjugated with carbonyl groups). These reaction is useful to visualize chromatogram (TLC).

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Color Reactions

- **Fluorescence Reactions:**
 1. Jensen reaction: Spraying the plates with trichloroacetic acid in solution in ethanol. The simultaneous use of an oxidant (chloramine T) allows the observation of fluorescent spots of different colors, which facilitates the interpretation of the chromatograms. Phosphoric acid can also be used, alone or mixed with sulfuric acid and ferric chloride.

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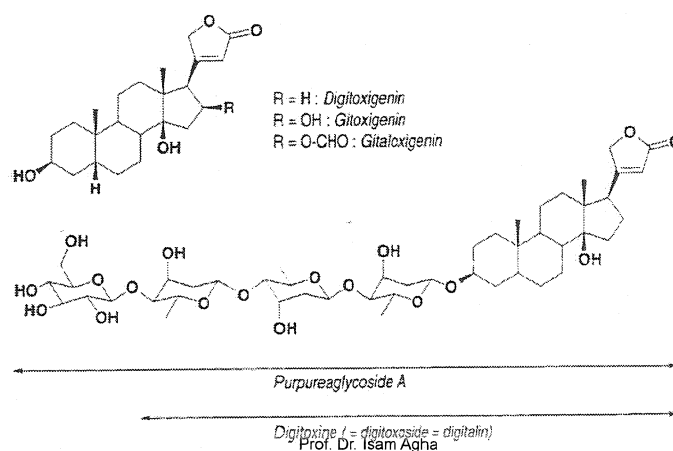
Quantitation

- Colorimetric method (Cardinolides): after Kedde reaction (lactone ring) or Baljet reaction.
- Changing in the max. Absorbance of the solution after adding alkaline (Bufadinolides).

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Aglycones and Cardinolides in Digitalis purpurea



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Alkaloids

Jean Bruneton
Pharmacognosy
790-798

الخواص الفيزيائية الكيميائية

Physico-chemical properties

- Alkaloids have molecular weights ranging from 100 to 900. للقلويدات لها وزن جزيئي.
- Most of the bases that do not contain oxygen atoms are liquid at ordinary temperatures (nicotine, sparteine, coniin). معظم الأسس غير الحاوية على أكسجين هي سائلة بدرجة الحرارة العادية.
- Alkaloids which contain oxygen atoms are crystallizable solids and in rare cases they are colored (berberine). القلويدات الحاوية على أكسجين متبلورة ومتلونة أحيانا قليلة.

الخواص الفيزيائية الكيميائية

Physico-chemical properties

- All of the crystallized bases rotate the plane of polarized light, and have sharp melting points, without decomposition, especially below 200° C. كل الأسس المتبلورة تحرف الضوء المستقطب لها درجة انصهار حادة ومحددة بدون تخرّب وخاصة دون 200 درجة مئوية
- Alkaloids as bases are not soluble or are sparingly soluble in water, soluble in apolar or only slightly polar organic solvents, and are soluble in concentrated hydroalcoholic solutions. القلويدات اسس غير ذوابة بالماء أو قليلة الذوبان بالماء ذوابة بالمذيبات العضوية أو بالمذيبات قليلة القطبية وذوابة في محاليل حمض الهيدروكلوريك

الخواص الفيزيائية الكيميائية

Physico-chemical properties

- The basicity of alkaloids varies greatly, since this property depends entirely on the availability of the lone pair of electrons on the nitrogen atom. تختلف اساسية القلويدات كثيرا وذلك اعتمادا على وجود زوج الكتروني على ذرة النيتروجين
- Electron-withdrawing groups in close proximity to the nitrogen atom decrease the basicity, whereas electron-donating groups enhance it: colchicine and piperine are, because of the presence of the carbonyl group on the amide, practically neutral. المجموعات الساحبة للالكترونات القريبة من ذرة النيتروجين تنقص من الاساسية، بينما المجموعات المانحة للالكترونات تعززها: الكولشيسين والبيبيرين معتدلة لوجود كاربونيل على الأמיד

الخواص الفيزيائية الكيميائية

Physico-chemical properties

- The basic character of alkaloids allows the formation of salts with mineral acids or organic acids. الخواص الأساسية للقلويدات تسمح بتشكيل أملاح مع الحموض العضوية أو المعدنية
- Alkaloid salts are generally soluble in water and in dilute alcohols, and they are, except in rare cases, not soluble in organic solvents. املاح القلويدات ذوابة في الماء وفي محاليل الكحولات الممددة، وهي غير ذوابة في المذيبات العضوية عدا بعض الاستثناءات

Detection and characterization

الكشف والتشخيص

- A detection technique ought to be, to the extent possible, rapid, simple, reproducible, and sensitive; it must be applicable to a small sample. يجب أن تكون طرق الكشف سريعة، بسيطة، قابلة للتكرار وقابلة للتطبيق

Detection and characterization

الكشف والتشخيص

- The general reagents for alkaloids are used. الكواشف العامة للقلويدات.
- The preliminary extraction can be a classic alkaloid extraction or an alcoholic maceration, which takes less time: the alcoholic solution is evaporated and the residue redissolved in acidic water; after filtering, the alkaloids are characterized in the filtrate. يستخلص بالكحول يكتف ومن ثم يعاد حل الناتج بالحمض الممدد. يرشح وتشخص القلويدات في الرشاحة

Detection and characterization

الكشف والتشخيص

- The general reactions of precipitation are based on the fact that alkaloids form combinations with metals and metalloids: Bismuth, mercury, tungsten, and iodine. التفاعلات العامة للترسيب تعتمد على تشكيل أملاح القلويدات معقدات مع الشوارد المعدنية
- solution of iodine and iodide, or a solution containing potassium iodide and mercuric chloride-known as Mayer's reagent-or a reagent containing bismuth nitrate and potassium iodide (daragendroff reagent) محاليل اليود، محاليل يوديد البوتاسيوم ومحاليل كلوريد الزئبق (كاشف مير) ومحاليل نترات البزموت ويوديد البوتاسيوم (دراجندروف)

Detection and characterization

الكشف والتشخيص

- It is also possible to use silicotungstic acid (mixture of tungsten and silicon oxides), or alkaline solution of iodoplatinates.
- The specificity of these reagents is not absolute: proteins, α -pyrones, some coumarins, hydroxyflavones, lignans, and other compounds can give false positive reactions with dragendroff reagent.

Detection and characterization

الكشف والتشخيص

- Other reagents are available to characterize alkaloids, particularly those that give color reactions characteristic of subgroups of alkaloids
- P-dimethyl-amino-benzaldehyde for the ergot alkaloids and pyrrolizidine alkaloids
- Cerium and ammonium sulfate, which differentiate indoles (yellow), dihydroindoles (red), B-anilinoacrylates (blue), oxindoles;

Detection and characterization

الكشف والتشخيص

- Ninhydrin for arylalkylamines
- The Vitali-Morin reaction for esters of tropic acid
- Reagents containing ferric chloride in the presence of hydrochloric acid (tropolones) or perchloric acid (Rauwolfia).
- The reactions listed above show the presence of alkaloids; but are not sufficient to verify the identity of a drug; they also do not provide information on the composition of mixtures.

Detection and characterization

الكشف والتشخيص

- To this end, and as in the case of many other secondary metabolites from plants, the methods currently used are TLC and HPLC, on normal or reverse phase (with solvents of the water-methanol or water –acetonitrile type).
- Dragendorff's reagent, the iodine-iodide solution (or iodine vapors), potassium iodoplatinate, or cerium and ammonium sulfate are commonly used to visualize TLC plates.

Extraction of alkaloids

استخلاص القلويدات

- The extraction of alkaloids is based, as a general rule, on the fact that they normally occur in the plant as salts and on their basicity, in other words on the differential solubility of the bases and salts in water and organic solvents.
- The plant material often contains substantial quantities of fats (this is particularly true for the seeds), and also waxes, terpens, pigments, and other lipophilic substances which may interfere with the extraction procedure, for example, by causing the formation of emulsions.

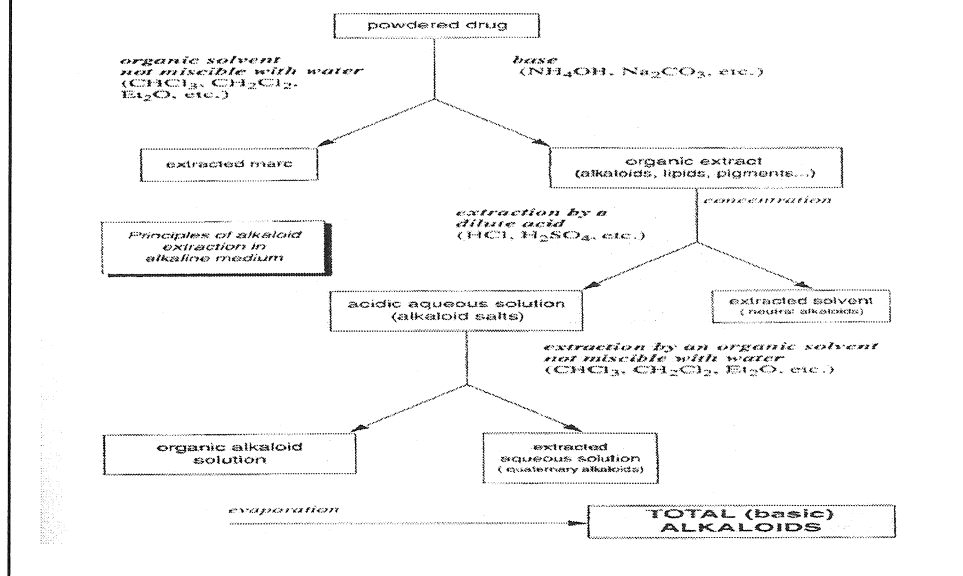
Extraction of alkaloids

استخلاص القلويدات

- These technical problems can be more or less completely avoided by preliminary defatting of the crushed drug.
- Petroleum ether and hexane are well suited for this step: alkaloids are soluble in these solvents only in exceptional cases, when the medium is neutral.

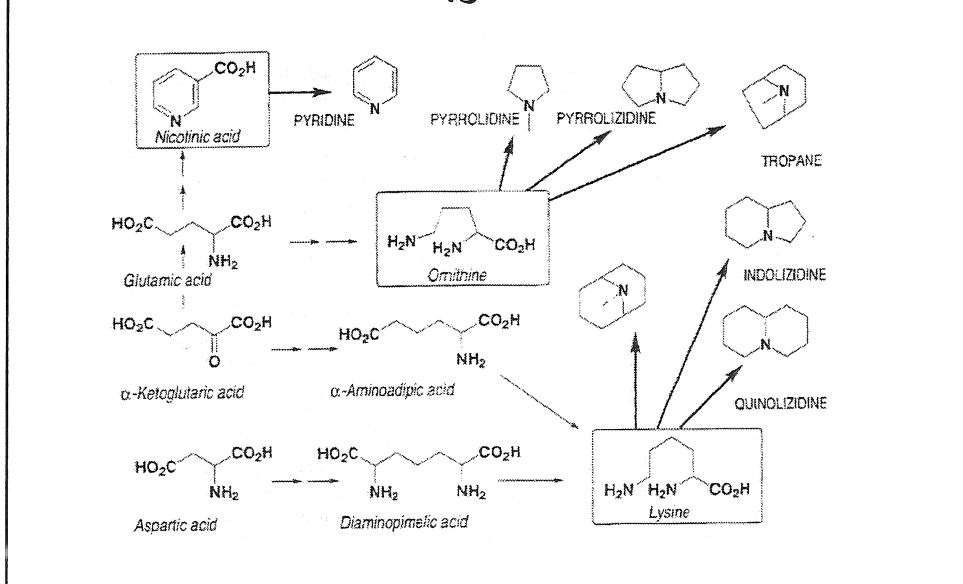
Solvent extraction

الاستخلاص بالمذيبات



Origin of some alkaloids

منشأ القلويدات



Origin of some alkaloids

منشأ القلويدات

